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## Guest Editorial

False negative studies may systematically contaminate the literature on the effects of inducers in  
neuropsychopharmacology. Part II: Focus on bipolar disorder

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**Running title:** False negative inducer studies part II

**Key words:** anticonvulsants; antipsychotic agents; antimanic agents; clobazam; clozapine; drug interactions; drug labeling; carbamazepine; olanzapine; oxcarbazepine; paliperidone; phenobarbital; phenytoin; quetiapine; risperidone; topiramate; valproic acid; vigabatrin.

This two-part editorial (part I focuses on epilepsy and part II focuses on bipolar disorder) proposes that the neuropsychopharmacology literature on drug-drug interactions (DDIs) which reports the effects of drug metabolic inducers is seriously contaminated not by false positives, but by false negative findings. Inducer effects are systematically denied or at least undervalued, and the available published literature systematically deemphasizes their clinical relevance. Moreover, this happens both in epilepsy and bipolar disorder literature where inducers increase the metabolism of many drugs metabolized by the Cytochrome P450 (CYP) and/or Uridine Diphosphate Glucuronosyltransferase (UGT) enzymes.

Next, this editorial proposes to demonstrate to the skeptical reader that a consistent pattern of denial and undervaluation of inducer effects exists in the neuropsychopharmacology literature. This pattern may be defined as systematic since it contaminates different pharmacological categories: (1) CYP3A4 drugs, (2) non-metabolized drugs, and (3) mild inducer drugs. Moreover, it contaminates the “narrative” of both epilepsy (see part I) and bipolar disorder (part II) pharmacological treatments which are characterized by polypharmacy, including the use of potent inducers such as carbamazepine or the more recently introduced mild inducers, such as oxcarbazepine.

From a historical perspective, denial and undervaluation of inducer effects usually occur first in the literature on antiepileptic drugs (AEDs) (see part I) and then in the literature on bipolar disorder (part II). Tiagabine is the best example of denial and undervaluation of inducer effects in a CYP3A4 drug among the AEDs (part I). Risperidone and quetiapine are examples of denial and undervaluing of inducer effects among the CYP3A4 drugs in bipolar disorder (part II). Topiramate and vigabatrin were briefly discussed (part I) as AED drugs allegedly not influenced by inducers since they are purportedly not metabolized. Paliperidone is discussed here (part II) as a bipolar disorder drug that is supposedly not metabolized. More attention is paid to the issues of mild inducer drugs since they have been almost completely neglected by prior literature. Among AEDs, topiramate, oxcarbazepine, clobazam and vigabatrin exemplify the denial and undervaluation of inductive effects of mild inducing drugs in epilepsy (part I), while valproate may be the best example of denial and undervaluation of mild inductive effects in

the bipolar disorder literature (part II). The section on mild inducers is the most extensive in parts I and II since they most clearly establish the pattern of false negative findings that has contaminated the literature for years. Only after companies were “forced” by the FDA to thoroughly study these drugs did it become clear that some of them are mild inducers. Since the literature lacks a review on mild inducers, the last section of part II compares the new findings on mild inducers with the literature on potent AED inducers.

## **DRUGS METABOLIZED BY CYP3A4 IN BIPOLAR DISORDER**

### **Risperidone**

Risperidone is mainly metabolized to an active metabolite, 9-hydroxyrisperidone, by CYP2D6. Risperidone was promoted as a CYP2D6 drug with none of the problems associated with CYP2D6 polymorphism, based on a study in volunteers published by Janssen<sup>1</sup> (see the review article<sup>2</sup> for the whole story on risperidone and the CYP2D6 polymorphism). Then a case report<sup>3</sup> proposed that risperidone must be metabolized by CYP3A4 since carbamazepine was an inducer of risperidone metabolism. Case series<sup>4,5</sup> and in vitro studies<sup>6,7</sup> verified that carbamazepine induces risperidone metabolism, mediated by CYP3A4 induction. Risperidone has affinity for the P-glycoprotein (P-gp) and its metabolite 9-hydroxyrisperidone (paliperidone) may have even higher affinity for P-gp.<sup>2</sup> CYP3A4 and P-gp appear to share substrates, inhibitors and inducers. Carbamazepine is believed to be not only a CYP3A4 inducer but also a P-gp inducer. Therefore, it is likely that P-gp induction may contribute to carbamazepine inductive effects in risperidone and its metabolite.

In 1997, during a risperidone poster presentation by the author,<sup>8</sup> people working at Janssen commented among themselves that “we know all of this”, leading the author to assume that the company was already familiar with CYP3A4’s role in risperidone metabolism by 1997. This knowledge of carbamazepine inducer effects on risperidone demonstrated by independent researchers (and possibly by the company researchers) did not lead to thoughtful planning for the risperidone randomized clinical trials (RCTs) in bipolar disorder since there was partial failure (in the carbamazepine arm) in an adjuvant risperidone RCT in mania designed by the company.<sup>9</sup> According to the author’s studies,<sup>10</sup> after correcting

for confounders, inducers such as carbamazepine are associated with a total risperidone concentration 59% lower than those in patients who were not on inducers. Therefore, to obtain a positive outcome in the carbamazepine arm, the company should have at least doubled the risperidone dose, compared with the non-induced risperidone dosages taken by the other manic patients (on lithium or valproate).<sup>11</sup> More recently a population pharmacokinetic study by Janssen verified that carbamazepine influences both risperidone and 9-hydroxyrisperidone levels in patients taking carbamazepine.<sup>12</sup>

## Quetiapine

The case of quetiapine is even more perplexing than that of risperidone, since information about the powerful effects of inducers on quetiapine metabolism was published by the company,<sup>13</sup> but the prescribing information (<http://dailymed.nlm.nih.gov/dailymed/lookup.cfm?setid=0584dda8-bc3c-48fe-1a90-79608f78e8a0>) did not include an explanation of these findings in a way that could be easily understood by clinicians. As details were provided before,<sup>14</sup> only two major factors are stressed here: (1) a company study<sup>13</sup> demonstrated that phenytoin increased quetiapine clearance by a factor of 5, and (2) the prescribing information did not recommend how to increase quetiapine dose to compensate for phenytoin induction. Increasing the dose by a factor of 5 should have been recommended.<sup>15</sup>

Quetiapine induction details are not well understood. A study indicated that thioridazine may also be a quetiapine inducer,<sup>16</sup> which is compatible with the observation that mesoridazine, the main thioridazine metabolite, may possibly be a risperidone inducer, as well.<sup>4</sup> Quetiapine is also a substrate of P-gp.<sup>17</sup> The relevance of P-gp versus CYP3A4 induction in quetiapine patients taking 1) potent inducers such as phenytoin<sup>13</sup> or carbamazepine<sup>18</sup> or 2) thioridazine<sup>16</sup> and/or mesoridazine is not currently understood.

## NON-METABOLIZED DRUGS IN BIPOLAR DISORDER

### Paliperidone

One needs to understand the risperidone story (see prior section) in order to understand the paliperidone story, since paliperidone is 9-hydroxyrisperidone, the risperidone active metabolite. When risperidone was marketed, articles by the company researchers<sup>19</sup> tended to deny the relevance of CYP2D6

polymorphism and of risperidone DDIs. When paliperidone was marketed, risperidone's greater potential for pharmacokinetic problems was finally acknowledged by company researchers. Sheehan et al.<sup>20</sup> stated, "The metabolism of risperidone by CYP2D6 or CYP3A4 results in potential CYP450-mediated pharmacokinetic drug-drug interactions when patients receive co-administered CYP2D6 inhibitors (e.g., fluoxetine, paroxetine, thioridazine), CYP3A4 inhibitors (e.g., ketoconazole), or CYP3A4 inducers (e.g., carbamazepine, phenytoin)" (page 522). And "Our AbsorptionDistributionMetabolismExcretion (ADME) analysis, which revealed paliperidone undergoes the least overall metabolism, combined with the literature review which demonstrated CYP450 enzymes have only a minimal role in the overall elimination of paliperidone, suggest paliperidone may be the least likely agent to be affected by a CYP450 interaction." (page 523). According to the company studies, paliperidone is subject to limited metabolism; therefore, it can be marketed to clinicians as a drug that is not metabolized and consequently without risperidone DDI problems. That risperidone is induced by carbamazepine may be a bad marketing story for risperidone, but it is a good one for paliperidone, assuming that paliperidone is not induced by carbamazepine. If this is true, this DDI should help to increase paliperidone use versus generic risperidone use in bipolar disorder.

According to paliperidone prescribing information

(<http://dailymed.nlm.nih.gov/dailymed/lookup.cfm?setid=7b8e5b26-b9e4-4704-921b-3c3c0d159916>)

"while *in vitro* studies indicate that CYP2D6 and CYP3A4 may be minimally involved in paliperidone metabolism, *in vivo* studies do not show decreased elimination by these isozymes and they contribute to only a small fraction of total body clearance. *In vitro* studies have shown that paliperidone is a P-gp substrate." The company study of paliperidone metabolism in 5 male volunteers who were given 1 mg of labeled paliperidone has been published.<sup>21</sup> In this study, approximately 60% of the compound was eliminated unchanged in the urine and the percentages were similar in subjects who were CYP2D6 poor metabolizers. Four paliperidone metabolic pathways were identified, each of which accounted for up to a maximum of 6.5% of the biotransformation of the total dose. The authors concluded that paliperidone is

not extensively metabolized and is primarily excreted renally.<sup>21</sup> A comparative review written by the company researchers<sup>20</sup> provides a more accurate description of this isotope paliperidone study.

Metabolism of paliperidone accounts for 20% of elimination since 20% of it may be eliminated unchanged in the urine in the average non-induced subject. That 20% of paliperidone is metabolized in non-induced subjects does not suggest to this author that paliperidone is “minimally metabolized.”

The company conducted a carbamazepine DDI study with paliperidone which is not yet published but is briefly described in the prescribing information. It indicated that adding 400 mg/day of carbamazepine to 6 mg/day of paliperidone “caused a decrease of approximately 37% in the mean steady-state C<sub>max</sub> and area under the curve (AUC) of paliperidone” and is explained “by a 35% increase in renal clearance of paliperidone. A minor decrease in the amount of drug excreted unchanged in the urine suggests that there was little effect on the CYP metabolism or bioavailability of paliperidone during carbamazepine co-administration.” Paliperidone doses “should be re-evaluated and increased if necessary including those after carbamazepine’s initiation; on the other hand, it “should be re-evaluated and decreased if necessary” after carbamazepine’s discontinuation. It is disconcerting that the lack of information on carbamazepine and paliperidone treatment duration obscures the clinical relevance of this study. If the 37% AUC increase reflects maximum induction, paliperidone dosing will not need to be modified but if reflects induction after only a few days of low doses of carbamazepine with a single dose of paliperidone, paliperidone dosing may need to be dramatically modified under steady state treatments. It is very worrisome that another company DDI paliperidone study, with paroxetine, appeared to be designed to provide negative findings by using very low doses of paliperidone (3 mg/day) and of the inhibitor, paroxetine (20 mg/day).<sup>22</sup>

If one believes that the effects of carbamazepine on paliperidone are not important, one would test its adjunctive effects in mania RCTs. However, the company did not use carbamazepine but lithium and valproate in adjunctive mania RCTs.<sup>23</sup> At any rate, paliperidone ER (3-12 mg/day) did not show statistically significant efficacy when added to valproate or lithium in a mania RCT.<sup>23</sup>



To conclude, it is important to remember that in non-induced subjects 20% of paliperidone is metabolized, according to the company review article,<sup>20</sup> but this percentage may be much higher (as occurs in topiramate) in patients taking inducers such as carbamazepine. The role of P-gp and/or CYPs in paliperidone excretion may be relatively higher than the 20% of the total metabolism in induced subjects.

## **MILD INDUCERS IN BIPOLAR DISORDER**

### **Valproate**

Valproate was approved as an AED in Europe in the 1960s,<sup>24</sup> introduced in the US in 1978, and approved for mania in 1995 before thorough pharmacokinetic studies were required by the FDA. Traditionally, valproate is considered a potential inhibitor<sup>24,25</sup> for some metabolic enzymes but not an inducer.  $\beta$ -oxidation is the most important valproate metabolic pathway in low doses but glucuronidation dominates in higher (including therapeutic) doses. In 2000, McLaughlin et al.<sup>26</sup> described rat studies in which high valproate doses could enhance valproate metabolism, and in a human felbamate study<sup>27</sup> including a valproate-only arm, data compatible with valproate induction of its  $\beta$ -oxidation was produced. Then they designed the first human study to test whether valproate was an inducer in 12 young healthy volunteers who took 400 mg/day of sodium valproate for 3 weeks. They found the urine metabolites resulting from the  $\beta$ -oxidation pathway increased from day 7 to day 21.<sup>26</sup>

In 2007, Cervený et al.,<sup>28</sup> encouraged by the rat data that valproate may be an inducer, conducted a human hepatocyte study that demonstrated that valproate may induce CYP3A4 and P-gp gene expression. Cervený et al.<sup>28</sup> proposed that this valproate induction may be relevant in patients with epilepsy and bipolar disorder. In fact, this induction may explain a prior study<sup>29</sup> that found that valproate may induce aripiprazole metabolism. Citrome et al.<sup>29</sup> studied 6 male patients taking 30 mg/day of aripiprazole for 2 weeks in whom valproate was titrated from 250 mg/day to a valproate level of 50 to 125 mg/L over 1 week. Aripiprazole geometric mean AUC decreased by 26% (and the metabolite by 7%) 3 weeks after starting valproate. This increased aripiprazole metabolism may be due to CYP3A4 and/or P-gp induction<sup>30</sup> if the in vitro study by Cervený et al.<sup>28</sup> is correct.

Small increases or decreases in clozapine levels in patients taking valproate are found in TDM.<sup>30,31</sup>

By using a statistical model in 255 clozapine patients (37 on valproate), Diaz et al.<sup>31</sup> found that valproate appeared to act as a mild clozapine inhibitor in non-smokers but as an mild inducer in smokers. Valproate inductive effects on clozapine may be dose-dependent, requiring high valproate doses.<sup>32</sup>

TDM studies found no valproate influence on olanzapine metabolism.<sup>33,34</sup> However, in four patients stabilized on olanzapine, valproate (1000-2700 mg/day) decreased olanzapine levels by 50% with a psychiatric deterioration in three of them.<sup>35</sup> In a prospective DDI study of 18 psychotic patients who had no relapses, valproate co-administration (600-2000 mg/day) was associated with a significant decrease in mean serum olanzapine concentrations from  $32.9 \pm 9.7$  ng/mL at baseline to  $27.4 \pm 9.8$  ng/mL at week 2, and to  $26.9 \pm 9.2$  ng/mL at week 4 probably explained by valproate induction on olanzapine metabolism by CYPs or UGT.<sup>36</sup> The changes in serum olanzapine concentration (1) were statistically significant, small and presumably not clinically significant; (2) varied with time (from 2 to 4 weeks) and with valproate concentrations; and (3) were compatible with valproate being an inducer of olanzapine metabolism but also a competitive inhibitor. Using a model to predict the effects on 10 mg/d of olanzapine at 4 weeks, valproate appeared to almost always behave as an inducer in smokers (unless valproate concentrations  $<13$  µg/ml) but in non-smokers valproate's competitive inhibition effects appeared to eliminate inductive effects on valproate concentrations  $<42$  µg/ml. Further studies are necessary to elucidate the mechanisms, severity and duration of this DDI and to understand whether there are any circumstances (e.g., high or low olanzapine or valproate doses) in which this DDI may acquire clinical relevance.<sup>37</sup>

The industry supported several RCTs combining olanzapine and valproate<sup>38</sup> but no olanzapine-valproate DDI studies. All the olanzapine studies indicating that valproate is an inducer were completed by independent investigators. The valproate prescribing information

(<http://dailymed.nlm.nih.gov/dailymed/lookup.cfm?setid=4619aff4-0f80-444f-858d-42e4137aa809>)

related to DDI does not include information on olanzapine but discusses a lack of DDI with clozapine,

based on a study of 11 psychotic patients, although the study design is not described. Olanzapine prescribing information (<http://dailymed.nlm.nih.gov/dailymed/lookup.cfm?setid=d5051fbc-846b-4946-82df-341fb1216341>) reports that olanzapine does not influence valproate pharmacokinetics, but did not refer to the effects of valproate on olanzapine.

In summary, the human literature before 2000 did not describe valproate as an inducer. Since then, an in vitro study and clinical studies on aripiprazole, olanzapine and clozapine indicate that valproate may behave as a mild inducer in some circumstances. Valproate inductive effects might not be clinically relevant unless high doses are used, but there has been no effort from pharmaceutical companies to further explore this issue with controlled studies using high valproate doses. As valproate is now a generic drug and second-generation antipsychotics are becoming generic, it will be up to the limited resources of non-industry researchers to definitively establish the relevance of valproate inductive effects for bipolar and other patients.<sup>37</sup> It is not known when valproate inductive effects reach maximum levels.

## **PHARMACOLOGY OF POTENT AND MILD AED INDUCERS**

This editorial does not try to extensively review what we know about mild AED inducers but uses them as the best example to prove that the literature has systematically deemphasized the role of inducers in epilepsy (see part I) and bipolar disorder (part II). Four mild AED inducers were reviewed: topiramate, vigabatrin, clobazam (part I) and valproate (part II). Three other AEDs<sup>30</sup> may also be mild inducers: lamotrigine may induce its own metabolism; felbamate, CYP3A4; and rufinamide, CYP3A4 and some UGTs. The data on these other three mild inducers is so limited that it is not worthwhile to explore whether their literature underestimates their inductive effects or not. This last section, by focusing on four mild inducers (topiramate, vigabatrin, clobazam and valproate), describes interesting pharmacological differences when mild inducers are compared with potent inducers. Three potent inducers, carbamazepine, phenytoin and phenobarbital, are briefly reviewed.

### **Potent Inducers**

Carbamazepine induces several metabolic enzymes including CYPs (CYP1A2, CYP2A6, CYP2B6, CYP2C9, CYP2C19, CYP3A4) and several UGTs.<sup>30,39</sup> The literature<sup>25</sup> usually concludes that induction starts in 1 week, maximal induction and de-induction occur in 3 weeks, and carbamazepine auto-induction takes 3-5 weeks.<sup>39</sup>

Phenytoin induces several metabolic enzymes including CYPs (CYP1A2, CYP2A6, CYP2B6, CYP2C9, CYP2C19, CYP3A4) and several UGTs.<sup>30,39</sup> Although it has not been systematically explored, the literature<sup>25</sup> usually states that phenytoin maximal induction or de-induction takes place in 1-2 weeks. Phenytoin is metabolized by CYP2C9 and CYP2C19, and if phenytoin is an inducer of the CYP2C subfamily, some auto-induction should be evident. It may not be easy to demonstrate since (1) inducers have major effects on some CYPs, particularly CYP3A4 and CYP2B6, but have only mild to moderate effects on the CYP2C subfamily;<sup>40</sup> and (2) phenytoin can easily saturate its own metabolism. However, Chetty et al.<sup>41</sup> demonstrated auto-induction under controlled conditions by showing that a third dose of 300 mg/day phenytoin was associated with lower AUC when compared with the first 300 mg/day dose in 18 male volunteers.

Phenobarbital induces several metabolic enzymes including CYPs (CYP1A2, CYP2A6, CYP2B6, CYP2C9, CYP2C19, CYP2E1, CYP3A4) and UGT1A1.<sup>30,39</sup> Although it has not been systematically explored, the literature<sup>25</sup> usually describes phenobarbital induction as starting in 1 week and maximal induction or de-induction occurring in 2-3 weeks.

Most of the time induction is mediated by intracellular receptors that may crosstalk.<sup>42</sup> Phenytoin and phenobarbital appear to bind to the pregnane X receptor (PXR), which regulates CYP2B, CYP2C and CYP3A subfamilies<sup>42</sup> as well as UGT1A1<sup>43</sup> and some transporters.<sup>44</sup> Carbamazepine, phenytoin and phenobarbital appear to bind to the constitutive androstane receptor (CAR), which regulates CYP2B, CYP2C and CYP3A subfamilies<sup>42</sup> as well as UGT1A1.<sup>43</sup>

## **Comparison with Mild Inducers**

The limited information on mild inducers indicates that at least topiramate<sup>45</sup> and valproate<sup>28</sup> may act using the same intracellular receptors as the potent AED inducers.

Although it has not been systematically studied, it is generally accepted that potent inducers tend to maximally induce most patients and the addition of other potent inducers may have no further effects. It is also usually believed that a therapeutic dose for epilepsy should cause induction in most patients. The limited available literature suggests that mild inducers appear to cause induction only in some patients, and that high doses may be required to detect the inductive effects. A confounding problem is that other pharmacological processes may obscure the inductive effects when studying mild levels of induction. Thus, it is possible that topiramate, clobazam and valproate induction may be obscured by inhibitory properties of these drugs, making it difficult to demonstrate their inductive effects. This may not be specific to the mild inducers, since it may occur with phenytoin and CYP2C induction that also only reaches mild levels.<sup>40</sup> The difference is that phenytoin is a potent inducer of other enzymes such as CYP3A4, and these other effects are hard to miss. In summary, low levels of induction by mild inducers or by phenytoin in CYP2C induction can easily be obscured by inhibition.

The most striking difference between mild and potent inducers is that, in several of them, induction may be a slower process than that of the potent inducers. Maximal induction and de-induction with potent inducers takes a matter of weeks, no more than 1 month. The marginal data that this editorial has reviewed on clobazam, oxcarbazepine, vigabatrin and valproate suggest that induction may require months (>1 month). This long duration has probably contributed to the difficulty of identifying mild inducers as inducers.

## CONCLUSION

This editorial was written with the hope of convincing the reader that the neuropsychopharmacology literature is contaminated by a systematic denial and underestimation of inducer effects. (1) Denial usually occurs first in the AED literature (part I) and then is repeated in the

literature on bipolar disorder (part II). (2) It cuts across pharmacological mechanisms, including CYP3A4 and non-metabolized drugs, and is more evident in the case of mild inducer AEDs.

The editorial also presents the case that the literature is misinformative regarding the clinical relevance of DDIs mediated by induction. Pharmaceutical companies have paid insufficient attention to this issue for a variety of reasons including the following: 1) more complicated study designs including longer duration are more expensive; 2) subtle effects from induction, which may not be apparent for up to 2 months, may be below the threshold of detection for many studies; and 3) the lack of regulatory direction and incentives have not encouraged the industry to fully explore induction as a variable influencing dosage regimen design before initial marketing. Fortunately, for drugs recently marketed in the US, the FDA requirements have helped to establish that “old” drugs that were not thought to be inducers, such as clobazam and vigabatrin, are mild inducers (see part I). The author has consistently expressed<sup>15,30,46,47</sup> for many years his view that the only easy way to orient clinicians to inductive effects is to provide average correction factors (e.g., to correct for these inductive effects, clinicians need to multiply the dose of the drug by 1.5, 2 or 5 times). This is not required by the FDA, but it is only fair to say that a few prescribing informations (or package inserts or drug labels) includes correction factors.<sup>2</sup> The two best examples are the prescribing information for lamotrigine (<http://dailymed.nlm.nih.gov/dailymed/lookup.cfm?setid=d7e3572d-56fe-4727-2bb4-013ccca22678>) and aripiprazole (<http://dailymed.nlm.nih.gov/dailymed/lookup.cfm?setid=c040bd1d-45b7-49f2-93ea-aed7220b30ac>), which indicate that doubling the dosage is needed to compensate for induction with potent inducers.

Finally, a review of the historical process of identifying the actions of mild inducers suggests that the underdetection and underestimation of mild inducers has not been solely an attempt to cover up this issue, but may also be partly explained by the possibility that these inductive effects may take longer than expected to reach maximum effects. If this is true, DDI studies of several months’ duration may be required to rule out mild inducers as having clinical relevance. It is possible that once we better

understand the complex process of induction, newer and simpler methods may help to identify future drugs as inducers. If this editorial is correct that the literature has stressed the false negative findings too much, a major practical problem remains: who should teach current prescribers how to handle inducers? The prescribers need to (1) address the major effects of potent inducers that are less frequently but not rarely used in epilepsy and bipolar disorder, and (2) be alert to the possibility that the mild AED inducers may be clinically relevant inducers for some of their patients with epilepsy or bipolar disorder.

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